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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/030,351	06/07/2002	. Stace Lindsay	06727/008002	8638

21559 7590 01/30/2008

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EXAMINER	
BERTOGLIO, VALARIE E	
ART UNIT	**PAPER NUMBER**
1632	

NOTIFICATION DATE	DELIVERY MODE
01/30/2008	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

patentadministrator@clarkelbing.com

Office Action Summary	Application No.	Applicant(s)	
	10/030,351	LINDSAY ET AL.	
	Examiner	Art Unit	
	Valarie Bertoglio	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *02 November 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,6,7 and 21-27* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) _____ is/are rejected.

7)☐ Claim(s) ____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *07 January 2002* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 11/02/2007 has been entered.

Claims 2-5 and 8-20 are cancelled. Claims 6,21 and 23 are amended. Claims 25-27 are added. Claims 1,6,7,21-27 are pending and under consideration in the instant office action.

Claim Rejections - 35 USC § 112-1st paragraph

Claims 6,7,21-24 and 27 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. 37 CFR 1.118 (a) states that "No amendment shall introduce new matter into the disclosure of an application after the filing date of the application".

Claims 6,21 and 23 contain the phrase "biologically active". Literal support for this terminology is not found in the specification. Applicant states at page 4 of the Remarks dated 11/02/2007 that support for the amendments can be found in the specification at pages 5, lines 8-11 and page 9, lines 12-17. However, the relevance of these passages is unclear and fails to support the amendments. Page 5 at lines 8-11 states "In various preferred embodiments of the ninth and tenth aspects of the invention, the method may be used for the treatment of cancer, for suppressing the immune system, or for inducing proliferation of bone marrow cells in a patient in need thereof." Page 9, lines 12-17 states, "By "therapeutically-effective amount" is meant an amount of recombinant human alpha-fetoprotein or fragment thereof that when administered to a patient inhibits or stimulates a biological activity modulated by human alpha-

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New Matter

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when administered to a patient inhibits or stimulates a biological activity modulated by human alpha-fetoprotein. Such biological activities include inhibiting the proliferation of a neoplasm or an autoreactive immune cell, or stimulating proliferation of a cell (e.g., a bone marrow cell)."

To the extent that the claimed compositions and/or methods are not described in the instant disclosure, claims 6,7,21-24 and 27 are also rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention, since a disclosure cannot teach one to make or use something that has not been described.

MPEP 2163.06 notes "If new matter is added to the claims, the examiner should reject the claims under 35 U.S.C. 112, first paragraph - written description requirement. In re Rasmussen, 650 F.2d 1212, 211 USPQ 323 (CCPA 1981)." MPEP 2163.02 teaches that "Whenever the issue arises, the fundamental factual inquiry is whether a claim defines an invention that is clearly conveyed to those skilled in the art at the time the application was filed. If a claim is amended to include subject matter, limitations, or terminology not present in the application as filed, involving a departure from, addition to, or deletion from the disclosure of the application as filed, the examiner should conclude that the claimed subject matter is not described in that application. MPEP 2163.06 further notes "When an amendment is filed in reply to an objection or rejection based on 35 U.S.C. 112, first paragraph, a study of the entire application is often necessary to determine whether or not "new matter" is involved. Applicant should therefore specifically point out the support for any amendments made to the disclosure" (emphasis added).

Written Description

Claims 25-27 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Vas-Cath Inc. v. Mahurkar, 19USPQ2d 1111, clearly states that "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession *of the invention*. The invention is, for purposes of the 'written description' inquiry, *whatever is now claimed.*" (See page 1117.) The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed." (See *Vas-Cath* at page 1116).

Claims 25-27 are specifically drawn to a non-glycosylated form of rHUAFP. In the instant case the claimed nucleic acid sequence or transgene modified to express rHuAFP in a non-glycosylated form encompassed by the claims lack a written description. The specification fails to describe what nucleic acids fall into this genus and it was unknown as of Applicants' effective filing date what substitutes would have the property of a non-glycosylated form of rHuAFP that would maintain all the necessary structural and functional characteristics of rHuAFP. The number of possible alterations to make a non-glycosylated and functional form of rHuAFP are large. The specification fails to provide the support for these possible alterations as it mentions non-glycosylation in only two passages of the specification. First at page 12, lines 25-26, it is merely prophetically mentioned that a transgene may be engineered to express a rHuAFP that is non-glycosylated. Second, at page 20, lines 18-22, the specification teaches a single substitution of N to Q at the single glycosylation site. No other substitutions or alterations are described and the specification offers no teachings such that one would know what changes would result in a functional non-glycosylated rHuAFP.

Applicant is reminded that *Vas-Cath* makes clear that the written description provision of 35 U.S.C. §112 is severable from its enablement provision (see page 1115).

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1,6,7,21-24 remain rejected and newly added claims 25-27 are rejected under 35 U.S.C. 103(a) as being unpatentable over Deboer (1997, US 5,633,076; IDS) or Clark (1994, US 5,322,775;IDS) or Lubon (1998, US 5,831,141; IDS) in view of Morinaga (1983, PNAS, Vol. 80, pages 4604-4608; IDS) and Bennett (1997, Breast Cancer Research and Treatment, Vol. 45, pages 169-179; IDS) for reasons of record set forth at pages 10-13 of the previous office action dated 03/22/2005.

Applicant has amended the preamble of claims 6,21 and 23 to require that the HuAFP be biologically active. Applicant argues that the art teaches away from "biologically active" rHUAFP being secreted from the milk as there are free fatty acids in the milk that are known to bind and alter certain properties of the AFP. Specifically, Applicant refers to the teachings of Vallette that fatty acids can inhibit estrogen binding to mouse and rat AFP (see page 8, paragraph 3 of Applicant's Remarks).

This argument is not persuasive for several reasons. First, that some property or properties of rHuAFP *may* be altered by binding or other natural interaction with some fatty acids in milk, does not indicate that all, if any, properties will be affected by the levels of specific fatty acids that are present in milk. Binding of a fatty acid as a ligand would be considered a natural property of AFP and it is not clear that this would be undesirable. It is also noted that Vallette teaches that the identity and quantity of fatty acids present is important in the inhibition of estrogen binding and thus such a variability in the effect of various fatty acids on AFP would likely hold true for other activities of AFP, making it unpredictable which, if any, activities of AFP would be altered in milk. Second, the study of Vallette consisted of an unnatural, in vitro situation of incubating AFP with free fatty acids. Neither Applicant nor Vallette provide a nexus between this study and what occurs in vivo in the mammary gland. The in vivo physiology is vastly different from an in vitro environment and the interactions that the free fatty acids may have with other proteins, as well as with AFP, differ.

Vallette teaches a change in affinity of HuAFP for estrogen in the presence of certain levels of specific fatty acids. Loss of this activity, in itself, does not teach away from the combination of references of Deboer or Clark or Lubon in view of Morinaga and of Bennett. Vallette does not provide any teachings relevant or specific to mammary epithelial cells. Thus, Vallette does not indicate a) that any activity would be affected in AFP in the milk or b) if estrogen binding were affected, that other desired activities would be irreversibly lost.

Similarly, Applicant argues at page 9, paragraph 1, that Haouriugi teaches that free fatty acids induce subtle specific changes in the binding of hormones to plasma proteins, including AFP. This argument is not persuasive. These subtle conformational changes observed in AFP in plasma, discussed by Haouriugi did not preclude the isolation and usefulness of isolating AFP from various sources ranging from E. coli and yeast, to amniotic fluid, liver, and human cord blood (see Al-Awqati *et al.*, 1978, **Clin Chim Acta**, 89:173-182; Chaturvedi *et al.*, 1998, **Prep Biochem Biotechnol,** 28:293-303). Thus, there is no indication what changes, if any, in the properties of AFP will occur when the AFP is produced in the mammary environment. In fact, as supported by the post-filing art, rHuAFP appears identical when isolated from milk of a transgenic mammal as compared to AFP isolated from human cord blood (see Parker, 2004, of record, page 151, paragraph bridging columns) and similarly when isolated from amniotic fluid in comparison to that isolated from fetal liver (see Al-Awqati, 1978). Parker also noted similar pharmacokinetics and functionality of the rHuAFP isolated from milk of a transgenic mammal and AFP isolated from cord blood (paragraph bridging columns at page 182-col. 2, paragraph 2).

Applicant also argues that Parmelee teaches that HuAFP has been found to contain a variety of fatty acids. The relevance of this argument is not clear. It appears what Applicant is demonstrating is that HuAFP binds various fatty acids and the identity of those fatty acids may vary according to the environment of the HuAFP, i.e. its source, blood, liver, yeast cells, milk etc. However, Applicant has not

established through the teachings available at the time of filing, that there are fatty acids present in milk that would render HuAFP recovered from the milk unusable.

Thus, it appears as though the characteristics of AFP may differ to some degree in any environment, however, these differences do not preclude its isolation and use from these various sources. Al-Awqati (1978) found slightly different properties for AFP isolated from fetal liver and amniotic fluid; however, these differences failed to alter the functionality of the resulting proteins (see pages 180-181). Thus, the Examiner fails to find that any of Vallette, Haourigi or Parmelee teach away from the instant invention.

Applicant also argues that there was no expectation of success in combining the reference of either of Deboer, Clark or Lubon with Morinaga and with Bennett. Applicant asserts that even if the Office disagrees that the prior art teaches away from the combination of references, there is no reasonable basis that Deboer, Clark and Lubon render obvious the claimed mammalian system to make any recombinant protein with a reasonable expectation of success. Applicant asserts that the teachings of KSR stating that a combination that is obvious to try might be obvious under 35 USC 103 is not the case here (page 10 of Applicant's Remarks). Applicant again states that neither Deboer, Clark or Lubon teach expression of rHuAFP in the milk of a transgenic mammal and that it is significant that none provide any reasonable expectation that rHuAFP could be successfully expressed in a biologically active form.

In response, Deboer, Clark and Lubon render making any protein of interest obvious in the absence of evidence to the contrary as each of these references teach the claimed technology with virtually any protein of interest, specifically reciting a range of proteins including serum albumin, immunoglobulins, Factor VIII, Factor IX, and alpha1-antitrypsin. Furthermore, AFP has been isolated from a number of sources including E. coli, yeast, cord blood and fetal liver and is active in each of these cases; thus specific teachings suggesting rHuAFP isolated from milk would not be active are necessary to support an argument that there was not a reasonable expectation of success at filing.

Applicant has only provided evidence demonstrating effects of some fatty acids on characteristics of HuAFP but has not raised significant doubt as to a reasonable expectation of success. Applicant continues to doubt the potential success in combining the references by way of teachings relating to difficulties in obtaining protein C from milk of transgenic mammals (page 11 of Applicant's Remarks). These difficulties center around the necessity of post-translational modifications that are necessary for full protein C activity, and which are not fully carried out by mammary epithelial cells. While the lack of post-translational modifications of proteins in mammary epithelial cells are of concern in making recombinant protein in milk, this would not be the case for rHuAFP, which has been made in both E.coli and yeast and has been found to be active despite a lack of post-translational processing. Parker *et al* (2004) state that, "Mouse and human AFP cloned into both Escherichia coli and bacu-lovirus had the same immunosuppressive properties as AFP isolated from human fetuses, suggesting that neither glycosylation of AFP nor any bound ligands are necessary for activity. Production of rHuAFP in yeast also gave protein that had identical immunoreactivity to fetal AFP (see page 178, col. 1, paragraph 1).

Thus, Applicant's arguments regarding the art teaching away from the combination of Deboer, Clark or Lubon with Morinaga and Bennett and a lack of reasonable success are not persuasive and the rejection is maintained.

Conclusion

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Valarie Bertoglio whose telephone number is (571) 272-0725. The examiner can normally be reached on Mon-Thurs 5:30-4:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Peter Paras can be reached on (571) 272-4517. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

/Valarie Bertoglio, Ph.D./
Primary Examiner
Art Unit 1632